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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,909	12/18/2001	Heather L. Davis	C1039/7058(HCL X04/19/02)	8458

7590 10/06/2005

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

Helen C. Lockhart
Wolf, Greenfield & Sacks, P.C.
Federal Resrve Plaza
600 Atlantic Avenue
Boston, MA 02210

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,909	DAVIS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8-13,20-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 8-13, 20-33, and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

6.0

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection on 15 July, 2005. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 12 April, 2005, has been considered.

Status of the Claims

Claims 1, 5, 8-13, 20-33, and 35 are currently under examination. No claim amendments accompanied the response.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1, 5, 8-13, 20-33, and 35 stand rejected under 35 U.S.C. ə 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed

invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claims have been amended to include the following limitation: "wherein the non-nucleic acid adjuvant is a **non-saponin** immune stimulating adjuvant". The crux of the statutory written description requirement is whether one skilled in the art, familiar with the practice of the art at the time of filing, would have found the later filed claimed limitations in the originally filed disclosure. *In re Wilder*, 736 F.2d 1516, 1520, 222 U.S.P.Q. 369, 372 (Fed. Cir. 1984). The specification clearly states (see p. 20) the following:

> "An immune stimulating adjuvant is an adjuvant that causes activation of a cell of the immune system. It may, for instance, cause an immune cell to produce and secrete cytokines. This class of adjuvants **includes** but is not limited to **saponins** purified from the bark of the Q. *saponaria* tree, such as QS21 (a glycolipid that elutes in the 21St peak with HPLC fractionation; Aquila Biophnrmaceuticals, Inc., Worcester, MA); **poly[di(carboxylatophenoxy)phosphazene** (PCPP polymer; Virus Research lnstitute, USA); derivatives of **lipopolysaccharides** such as monophosphoryl lipid A (MPL; Ribi Immunochem Research Inc., Hamilton, MT), muramyl dipeptide (MDP; Ribi) and threonyl-muramyl dipeptide (t-MDP,Ribi); 0M-174 (a glucosnmine disaccharide related to lipid A; OM Pharma SA, Meyrin, Switzerland); and ***Leishmania* elongation factor** (a purified *Leishmania* protein; Corixa Corporation, Seattle, WA)."

Thus, the skilled artisan would reasonably conclude that applicants contemplated using a large genus of non-nucleic acid adjuvants. However, the skilled artisan would **not** reasonably conclude from the teachings of the specification that applicants contemplated an immunization method that employed a "non-saponin immune stimulating adjvuant". **The term is absent from the disclosure and nothing in the specification would lead the skilled artisan to this limitation.** Accordingly, the skilled artisan would reasonably

conclude that applicants were not in possession of the claimed invention at the time of filing.

Applicants cite *In re Johnson*, 558 Fed.2d. 1008, C.C.P.A. 1977, and argue that when both a genus and subgenus are disclosed, claims excluding the subgenus are adequately supported. This argument is not persuasive. First, the fact pattern in *In re Johnson* differs considerably from that of the instant application. The court was deciding the validity of a 35 U.S.C. § 112, second paragraph, rejection, and an enablement rejection under 35 U.S.C. § 112, first paragraph. Thus, the courts were not even considering issues directed toward new matter. Second, the crux of the rejection is whether or not applicants were in possession of the claimed subject matter. The disclosure provides a lengthy list of desired adjuvants, however, the disclosure does not discuss a sub-genus of poorly defined adjuvants that simply exclude one type of species. For instance, if the claim language included the list of adjuvants set forth on page 20, and in response to prior art or other issues removed the reference to saponin-based adjuvants, the claims would be acceptable. However, simply reciting a large genus that excludes a single species without providing any further representative species in the claim language would not lead the skilled artisan to that particular negative limitation. Accordingly, the rejection is proper and hereby maintained. Applicants may obviate the rejection by appropriate amendment of the claim language.

Written Description

Claims 1, 5, 8-13, 20-33, and 35 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at

the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *University of Rochester* v. *G. D. Searle & Co., Inc.*,, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. **The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of modified nondescript CpG dinucleotides, non-saponin adjuvants, and antigen.** An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate

written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). **The court noted in this decision that a laundry list disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.**

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. **The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely.** In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California*

v. Eli Lilly, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claimed invention suffers from a number of deficiencies. The disclosure describes a synergistic adjuvant effect between a combination of a single immunogen (HBSAg), single non-saponin adjuvant (e.g., alum), and a limited number of CpG dinucleotides (ODN #1826, 2006, 1968). Thus, the skilled artisan would reasonably conclude that applicants were in possession of this particular embodiment. However, the claimed subject matter contains an inordinate number of combinations of antigen/immunogen, adjuvant, and modified CpG ODN. It has been well-established in the vaccine art that identifying a suitable combination of immunogen and adjuvants is an empirical process. The skilled artisan cannot reasonably predict which combination will produce a synergistic effect. The specification provides a long laundry list of various immunogens, adjuvants, and CpG ODNs. The claim language encompasses an inordinate number of combinations. However, other than the particular embodiment discussed *supra*, nothing in the specification would lead the skilled artisan to any particular combination of immunogen, adjuvant, and CpG ODN. Moreover, the disclosure fails to provide sufficient structural guidance pertaining to the selection of suitable immunogens, adjuvants, and CpG ODNs that will display the desired synergistic responses. Accordingly, the skilled artisan would reasonably conclude that

applicants were not in possession of the claimed invention at the time of filing.

Enablement

Claims 1, 5, 8-13, 20-33, and 35 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As previously set forth, the claims are broadly directed toward methods for the induction of antigen-specific immune responses in a subject through the administration of antigen and a combination of adjuvants comprising a CpG dinucleotide and a non-saponin immune stimulating adjuvant (e.g., MPL). The disclosure provides a limited working embodiment involving a single antigen/immunogen (e.g., HBSAg) and adjuvant (e.g., Alum), and a limited number of CpG ODNs (e.g., #1826, #2006, #1968). Appropriately drafted claim language directed toward this embodiment would be acceptable. However, the specification does not support the full breadth of the claimed subject matter.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and

the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the structural requirements of any given "modified" ISS-ODN. The skilled artisan would require a knowledge of those sequences that should be included in any given ISS prior to practicing the invention. However, the disclosure fails to provide sufficient guidance pertaining to the composition and length of those sequences that produce a synergistic immune response when combined with another adjuvant. Moreover, various phosphate backbone modifications can have unpredictable effects on the adjuvant activities of any given CpG ODN. What type of phosphate backbone modifications result in retention or improvement of the adjvuant activities of any given CpG ODN? The disclosure and applicants' arguments fail to provide any guidance pertaining to this issue.

2) The disclosure fails to provide adequate guidance pertaining to those immune stimulating adjuvants (e.g., saponins, MPL, MDP, etc.) that can reasonably be expected to produce a synergistic immune response when combined with a modified CpG ODN adjuvant. Vaccine development is an empirical process that requires extensive experimentation to identify suitable combinations of immunogen and adjuvant(s), routes of inoculation, and immunization regimens. Moreover, the claims require a synergistic effect from combining the CpG-containing ISS and other non-nucleic acid adjuvant. As previously set forth, while the declaration of Dr. Hunter provided some evidence for a synergistic immune response between a specific combination of CpG ODN, adjuvant, and immunogen (e.g., CpG-1826, alum, and HBSag), it also demonstrated that many combinations of ISS, adjuvant, and immunogen were **not** synergistic. Thus, the

skilled artisan would still needs to know which combination of CpG-ODN, non-nucleic acid adjuvant, and immunogen should be employed. **3) The prior art is unpredictable and teaches that many putative ISS elements do not function in the manner desired and often fail to facilitate immune responses to the immunogen of interest.** Moreover, the skilled artisan cannot reasonably predict which combination of adjuvants will have a synergistic effect when employed concomitantly. The effectiveness of any given preparation will depend upon several factors including the antigen, adjuvants, dose, immunization regimen, and site of immunization. Because of the empirical nature of this process, the skilled artisan cannot reasonably predict which combinations of adjuvants will display synergistic effects when administered concomitantly with an immunogen. This is not surprising considering the complexity of the immune system. As set forth *supra*, the declaration of Dr. Hunter delt primarily with a single ISS, CpG-1826. Thus, it failed to directly address this point.

4) The claims are of considerable breadth and are not fully supported by the disclosure. The broadest claims are not limited to any particular CpG-ODN or immune stimulating adjuvant or immunogen. Accordingly, the claims literally encompass an inordinate number of combinations of immunogen, non-saponin adjuvant, and CpG ODN. However, the disclosure, declaration, and applicants' arguments fail to teach which combination(s) of immunogen, CpG-ODN, and adjuvant will produce the desired synergistic immune response.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

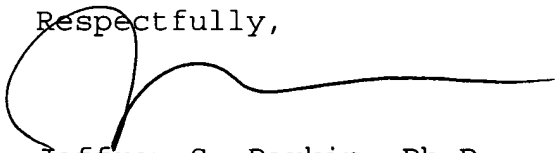
Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

02 October, 2005